SUMMARY IN ENGLISH

The introduction of antibiotics in the 1940s has contributed greatly to the treatment of infectious diseases. However, with its increased use both in humans and in livestock (selection pressure), the number of bacterial species that has become resistant to antibiotics, so-called multidrug-resistant bacteria, is growing. At the same time, the development of new antibiotics is gradually decreasing. And once multidrug-resistant bacteria have emerged they are able to spread further. This spread is facilitated, among others, by global travel, the food chain, and the hands of care providers in the treatment of patients. The emergence and further spread of multidrug-resistant bacteria combined with the scarcity of new antibiotics poses a serious threat to public health. In some parts of the world the resistance problems have even advanced to the stage where an infectious disease can lead to a patient’s death. Effective antibiotic medicines are simply no longer available.

This thesis consists of retrospective studies in the field of multidrug-resistant bacteria in the clinical setting. These studies illustrate a number of aspects of the resistance problems that we are faced with today.

Multidrug-resistant bacterial species with greatly reduced therapeutic options, such as New Delhi Metallo-beta-Lactamase 1 (NDM-1) and multidrug-resistant Acinetobacter baumannii (MDR-AB), are still rare in the Netherlands as opposed to some foreign countries where the presence of these bacteria is sometimes endemic. But as chapters 2 and 3 will show, the Netherlands can also not be spared the threat of these bacteria.

Chapter 2 describes a patient admitted in a Dutch hospital in August 2008 from whom an NDM-1-producing isolate was obtained. NDM-1 was first identified from a Klebsiella pneumoniae bacterium at the beginning of 2008 in an Indian patient who had returned from a hospital in India (hence the name) and was then admitted in a Swedish hospital. The Indian continent subsequently turned out to constitute a large reservoir for NDM-1 from where its worldwide spread would take place. Another patient described in chapter 2 had been referred from the intensive care department in a Serbian, not an Indian, hospital in Belgrade. Serbia is part of the Balkan region and forms, a second reservoir for NDM-1, as has since become apparent. This case illustrates that NDM-1 was already present in the Netherlands through import from endemic areas at about this same time. The identification from the frozen isolate could however only take place at a later time, after the necessary methodologies had become available.

A similar case where a multidrug-resistant bacterium was imported when a patient was transferred from a hospital in an endemic region is described in chapter 3. This case involves a patient with MDR-AB who had been repatriated from a Turkish hospital to a Dutch hospital. MDR-AB is endemic in Turkey, among other countries. This case shows yet again that MDR-AB is able to break through isolation precautions and disseminate, which may even result in the shutdown of an affected department.
Chapter 4 describes resistance problems that are not import-related but caused by antibiotic selection pressure combined with the transfer of resistant bacteria among patients in an intensive care unit (ICU). Here the impact of Selective Digestive Decontamination (SDD) on the occurrence of multidrug-resistant bacteria is discussed. Traditionally, SDD is used as prophylaxis to prevent ventilator-associated pneumonia in mechanically ventilated ICU patients, especially in the Netherlands. The idea is that SDD will (virtually) eliminate the potentially pathogenic micro-organisms in the gastrointestinal tract to prevent them from causing infections. A number of Dutch studies shows that the use of SDD in preventing ICU infections in a setting with low-prevalence multidrug resistance has a favorable effect on both morbidity and mortality. A disadvantage that has been mentioned, however, is the potential emergence of antibiotic resistance. In the study described in chapter 4 SDD was not used prophylactically but with the aim to eliminate the bacterial strain that was causing an outbreak of ESBL-producing Klebsiella pneumoniae (ESBL-Kp) bacteria. This aim was not achieved. Furthermore, the study shows that the prevalence of resistant bacteria, which were also resistant to SDD, increased and were even isolated from the blood of patients who had been treated with SDD. Upon discontinuation of SDD, restoration of the increased prevalence of multidrug-resistant bacteria was measured. This study shows that SDD should be used prudently and be applied judiciously, based on the results of the surveillance cultures.

The follow-up studies described in chapter 5 refers to the observation that all stored ESBL-Kp isolates obtained prior to the administration of SDD and re-tested with the E test were colistin-susceptible, whereas a large portion of these isolates obtained after the administration of SDD were colistin-resistant. This turned out to be caused by hetero-resistance: colistin-resistant variants of ESBL-Kp isolates may be present in such small amounts in the tested culture that they are not detected during routine antimicrobial susceptibility testing of colistin. This underlines the need to include a method for detection of colistin hetero-resistance in routine diagnostics.

Chapter 6 describes a different mechanism of drug resistance, namely plasmidal AmpC beta-lactamase (pAmpC). pAmpC is relevant in the clinical setting for two reasons: 1) it is present in the open population from where it can be introduced in clinical care; 2) it may be missed during routine diagnostic testing as no specific screening and confirmatory test methods are available. As a result, patients infected with pAmpC-carrying bacteria may not receive adequate antibiotic treatment.

In chapter 7 the course of the spread of multidrug-resistant bacteria in an intensive care department is described, as well as the challenges this department and the hospital were consequently faced with, and the effective role of the single room design of the ICU in containing this spread.

This thesis concludes that from the ‘One Health’ policy perspective, coordinated care networks are required to adequately fight antibiotic resistance in clinical care.